Klinefelter's Syndrome Accompanied by Mixed Connective Tissue Disease and Diabetes Mellitus

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We report a rare case of Klinefelter's syndrome (KS) with mixed connective tissue disease (MCTD), diabetes mellitus (DM) and several endocrine disorders. A 57-year-old man presented with polyarthritides and tapering fingers with Raynaud's phenomenon on admission. In addition to a karyotype of 47, XXY, a marked restrictive change in respiratory functional test, a myogenic pattern in electromyogram, the positive tests for anti-RNP antibody indicated that this was a case of KS complicated with MCTD. The patients also presented DM with insulin resistance, hyperprolactinemia, slight primary hypothyroidism and hypoadrenocorticism. The mechanism for these coincidences remains to be elucidated.

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Key words: insulin resistance, hypothyroidism, hypoadrenocorticism

Introduction

Klinefelter's syndrome (KS) is characterized by small, firm testes, azoospermia, gynecomastia, and elevated levels of plasma gonadotropins in men with two or more X chromosomes. This syndrome is well recognized to be associated with autoimmune disease (1), such as systemic lupus erythematosus (SLE) (2, 3), progressive systemic sclerosis (PSS) (4, 5) and polymyositis (PM) (6). On the other hand, it has also been accepted that the incidence of diabetes mellitus (DM) is high in patients with KS (7, 8). We recently treated a patient with KS associated with mixed connective tissue disease (MCTD) and DM. In order to gain insight to understand the pathogenesis of these diseases associated with KS, we performed several endocrinological and immunological studies and a glucose clamp test on this patient. Here, we report the case and results of these studies.

For editorial comment, see also p 838.

Case Report

A 58-year-old man was admitted to the Nagoya National Hospital on August 9, 1996, because of hyperglycemia, diarrhea and dehydration. The clinical course of this patient is summarized in Fig. 1.

In brief, about 40 years before admission, he was diagnosed as having SLE and had been treated with prednisolone from 1971 to 1991. In 1986, he complained of thirst and dry eyes and was admitted to the hospital where Sjögren's syndrome was suspected. During admission, DM was also diagnosed and insulin therapy was initiated, however, insulin therapy was stopped two years after for an unconfirmed reason. Since then, his blood glucose level was elevated and sulfonylurea was prescribed in 1992. In 1995, MCTD was suspected by a positive titer to anti-ribonucleoprotein (RNP) antibody. The blood glucose level also was elevated and he manifested hyperglycemic symptoms with diabetic enteropathy, such as diarrhea and abdominal pain. Insulin therapy was planned again and he was admitted to this hospital.

He was unmarried and had been unemployed. He had a history of gonarthrosis and cervical osteochondrosis treated with nonsteroid anti-inflammatory drugs. He had suffered from herpes zoster twice in 1978 and 1983, had operations for cataract twice at the ages of 55 and 57. As shown in Fig. 2, his mother, elder sister and brother had also diabetes mellitus (type 2 DM). An elder sister had been diagnosed for aortitis syndrome and a niece, for some type of collagen disease (further information not available).

On physical examination, his height was 162 cm with an arm span of 154 cm, and body weight 53 kg (Fig. 3). He had decreased body hair with female escutcheon, gynecomastia and

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Figure 1. Clinical course of the patient.

Figure 2. Family tree.

Figure 3. The patient with clinical features of decreased body hair and gynecomastia.

atrophied testes. He also presented with "tapering fingers" - edematous dorsum manus and slim fingers. His extremities were cold and Raynaud's phenomenon was noted. Neither goiter nor lymphadenopathy was found. The examination on chest and abdomen was normal.

Laboratory findings on admission are summarized in Table 1. Mild elevation of blood urea nitrogen probably due to dehydration was noted. Both fasting plasma glucose (FPG) and hemoglobin A_{1c} (HbA_{1c}) were elevated. Urinalysis was normal except for an increased excretion of microalbumin. These data indicate that DM in this patient had been poorly controlled. Results of endocrinological examination are summarized in Table 2, findings of hypergonadotropic hypogonadism were obtained. Basal levels in luteinizing hormone (LH) and follicle stimulating hormone (FSH) were elevated while serum concentrations of testosterone and dehydroepiandrosterone sulfate (DHEA-S) were low. Although serum free thyroxine (FT₄) and free triiodothyronine (FT₃) were within the normal range, basal TSH levels were slightly elevated and TSH response to TRH was exaggerated, indicating slight primary hypothyroidism. Slight primary hypoadrenocorticism was also noted with increased basal ACTH and decreased urinary ex-

cretion of cortisol, albeit a normal circadian rhythm of ACTH and serum cortisol level. Hyperprolactinemia was observed on August 14, 1996, but the level became within normal range on the second admission (February 16, 1998). Magnetic resonance imaging (MRI) showed that the anterior pituitary was slightly enlarged in the upward direction (Fig. 4).

According to chromosomal analysis showing that his karyotype was 47, XXY (Fig. 5) and the presence of hypergonadotropic hypogonadism, the diagnosis of KS was made.

He was also suspected to have a collagen disorder. A chest X-ray and computed tomography (CT) failed to detect findings of lung fibrosis, however, a marked restrictive change in respiratory functional test was observed; VC: 31%, FEV1.0: 114.2%. The echocardiogram showed no evidence of pulmonary hypertension, and the abdominal ultrasonography failed to show an anomaly in the kidney. The Schirmer test revealed decreased secretion of tears. Sialography showed atrophic salivary ducts without the findings of apple tree lesion. Lip biopsy was performed and histological findings compatible with Sjögren's syndrome were obtained. Serological tests for collagen diseases are summarized in Table 1. He was positive for anti-ribonucleotide protein (RNP) antibody and anti-nuclear

Table 1. Laboratory Results on Admission

Urine analysis		Immunological and Serological test	
protein [-]	glucose [-]	ketone body [-]	IgG 1,729 mg/dl (800–1800)
microalbumin	107 mg/g	CRE (15 $\geq$)	IgA 119 mg/dl (160–350)
			IgM 53 mg/dl (80–160)
Complete Blood Cell Count		Rheumatoid factor 5 U/ml (20 $\geq$)	
WBC	6,300/mm ³	Antinuclear antibody (+)	
RBC	404 $\times$ 10 ⁴ /mm ³	(Homogeneous and speckled)	
Hb	12.0 g/dl		
Ht	36.2%		
Platelet	28.2 $\times$ 10 ⁴ /mm ³	Anti-ss DNA	16.1 AU/ml (25 $\geq$)
Blood Biochemistry		Anti-nRNP	18.3 U/ml (Cut off index 15.0 $\geq$)
TP	7.5 g/dl	Anti-Sm	3.8 U/ml (Cut off index 15.0 $\geq$)
Alb	4.4 g/dl	Anti-SS-A	2.7 U/ml (Cut off index 20.0 $\geq$)
AST	13 IU/l	C _{3c}	82 mg/dl (55–120)
ALT	8 IU/l	C ₄	36 mg/dl (20–50)
ALP	159 IU/l		
LDH	450 IU/l		
BUN	25 mg/dl		
Cre	0.93 mg/dl		
Na	140 mEq/l		
K	4.3 mEq/l		
Cl	103 mEq/l		
Ca	9.7 mEq/l		
P	4.0 mEq/l		
CPK	71 IU/l		
24CCr.	76.2 ml/min		
FPG	286 mg/dl	Anti-GAD	4 $\geq$ U/ml (Cut off index 5.0 $>$)
HbA _{1c}	12.4%		

() normal range. TP: Total protein, Alb: Albumin, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, LDH: Lactate dehydrogenase, BUN: Blood urea nitrogen, Cre: Creatinine, 24CCr.: 24-hour creatinine clearance, FPG: fasting plasma glucose, HbA_{1c}: glycohemoglobin A_{1c}, RNP: ribonucleoprotein antibody, GAD: glutamic acid dehydrogenase.

antibody with homogeneous and speckled pattern. The other antibodies representing collagen diseases were negative. Serum complement levels were within the normal range. MCTD was diagnosed according to the criteria proposed by the Ministry of Health and Welfare, Japan; presence of Raynaud's phenomenon, positive tests for anti-RNP antibody, a finding of restrictive ventilatory defect, and a myogenic pattern in electromyogram as observed in polymyositis (data not shown).

Subsets of peripheral lymphocytes are shown in Table 3. The average CD3 counts which represents the total T cells was within the normal range. Ratio of the helper T cell (CD4) population to that of the suppressor T cell (CD8) was also normal. Populations of the total B cell and the total natural killer cell (NK) were normal.

The patient was diabetic with complications of simple retinopathy and several neuropathies. The presence of microalbuminuria also suggested the complication of nephropathy at an early stage although it was possibly manifested by MCTD. As shown in Table 4, an oral glucose tolerance test showed a DM pattern with a delayed secretion of insulin. Urinary excretion

of C-peptide was slightly decreased on admission, however, a glucagon infusion test performed on admission revealed a normal response of insulin secretion. These findings were compatible with type 2 DM. On admission, the glucose infusion rate (GIR) calculated from a normal glucose clamp test showed some resistance to insulin in this patient. Insulin was initiated again during his admission in 1996 by subcutaneous injection. Following the discharge, his body weight increased from 53 kg to 57 kg over one and a half years and his blood glucose levels gradually became elevated. On admission in 1998, the glucose clamp test was performed again and showed his insulin resistance did not improve and had worsened.

Discussion

Dysfunction of the hypothalamus, pituitary, thyroid and endocrine pancreas, in addition to the manifestation of gonadal insufficiency, have been recognized in KS (9). In the current case, the patient presented mild primary hypothyroidism, primary hypoadrenocorticism and hyperprolactinemia. In patients

Table 2. Endocrinology Results

	'96 Aug. 14	'98 Feb. 16	(normal ranges)
LH (mIU/ml)	42.1	41.3	(1.8–5.2)
FSH (mIU/ml)	91.9	76.8	(2.9–8.2)
ACTH (pg/ml)	83	82	(9–52)
PRL (ng/ml)	24.6	5.6	(1.7–10)
GH (ng/ml)	2.22	2.88	(0.42≥)
TSH (μU/ml)	5.47	7.44	(0.23–4)
Free T ₃ (pg/ml)	4.4	4.7	(3.8–6.1)
Free T ₄ (ng/dl)	1.1	0.9	(0.9–1.9)
anti-thyroglobulin antibody	×100>	–	(×100>)
anti-thyroid microsome antibody	×100>	–	(×100>)
TRAb (%)	0.0	–	(15≥)
ADH (pg/ml)	1.9	2.4	(0.3–3.5)
serum cortisol (μg/dl)	11.2	12.6	(6–20)
urinary cortisol (μg/day)	24.8	26	(30–100)
urinary 17-OHCS (mg/day)	3.7	7.2	(3.4–12)
urinary 17-KS (mg/day)	4.9	7.6	(4.6–18)
urinary aldosterone (μg/day)	2.4	–	(10≥)
serum testosterone (ng/dl)	145	–	(250–1,100)
intact PTH (pg/ml)	41	–	(15–50)
serum DHEA-S (ng/ml)	296	–	(400–3,500)

diurnal variation

	0600h	1200 h	1800 h	2200 h
GH (ng/ml)	0.42	0.06	0.09	0.4
ACTH (pg/ml)	94	38	20	11
cortisol (μg/dl)	11.8	5.2	2.5	0.6

provocative tests for anterior pituitary hormones
(LH-RH+CRH+TRH+GRH)

	before	15 min	30 min	60 min	90 min
LH (mIU/ml)	40.3	69.2	97.6	131	137
FSH (mIU/ml)	81.1	83.1	91.6	107	110
ACTH (pg/ml)	66	120	120	120	91
cortisol (μg/dl)	8.6	11.4	12.1	13.1	9.9
TSH (μU/ml)	3.4	29	46	43	36
GH (ng/ml)	0.14	8.97	6.96	9.40	10.4
PRL (ng/ml)	18.9	112	105	81	60

on admission : Aug.'96

on readmission : Feb.'98

LH: luteinizing hormone, FSH: follicle stimulating hormone, ACTH: adreno corticotrophic hormone, PRL: prolactin, GH: growth hormone, TSH: thyroid hormone stimulating hormone, TRAb: thyroid receptor antibody, ADH: antidiuretic hormone, 17-OHCS: 17-hydroxycorticosteroid, 17-KS: 17-ketosteroid, PTH: parathyroid hormone, DHEA-S: dehydroepiandrosterone-sulfate.

with KS, co-existing hypothyroidism has been reported sporadically (10–12). A number of studies have tried to find a possible underlying disorder in the hypothalamo-pituitary-thyroid axis in patients with KS. However, those reports were contra-

dictory and failed to locate a unique defect in the axis. Therefore, it indicates that the latent or subclinical hypothyroidism due to pituitary or hypothalamic defects, if present, are not universal in patients with KS (13). The patient in the current

Figure 4. Head MRI shows slight enlargement of anterior pituitary.

report presented normal FT_3 but subnormal FT_4 . Since a slightly high level of TSH with exaggerated response to TRH was observed, this patient possibly had mild thyroid dysfunction due to primary thyroid abnormalities. A goiter was absent and thyroid autoantibodies were negative, so the etiology of the thyroid abnormality in this patient remains to be elucidated. The patient also showed a slight primary hypoadrenocorticism. Urinary excretion of cortisol and serum DHEA-S decreased with a slightly elevated ACTH level. As far as we know, the complication of hypoadrenocorticism in patients with KS is rare. Atrophy of adrenocortex due to the treatment with prednisolone was unlikely, because when we examined the adrenal function, approximately five years after cessation of the treatment, he did not show any episode of adrenocortical crisis. The evaluation of autoantibodies against the adrenal cortex may provide insight into the etiology of the mild primary hypoadrenocorticism in this patient. The PRL level was elevated with a slight over-response to TRH in the examination carried out in 1996. Estrogen is known to augment PRL secretion (14). Hsueh et al (9) reported that the response of PRL secretion to TRH is variable in KS probably due to a variable increase in testosterone to estrogen conversion in KS. An increased estro-

Figure 5. Karyotype of the patient shows XXY pattern.

Table 3. Lymphocyte Subsets in the Peripheral Blood

Average CD3	Total T [CD3+] Lymphocytes	66%	(59.4–84.6)
Sum of Cells	T+B+NK	98%	(95–105)
Ratio	CD4/CD8	1.39	(0.9–3.6)
CD3/CD19	Total B cells [CD19+] Lymphocytes	25>>	(6.4–22.6)
CD3/CD4	T Helper cells [CD3+, CD4]	39%	(28.5–60.5)
CD3/CD8	T Suppressor cells [CD3+, CD8+]	28%	(11.1–38.3)
CD3/CD16+CD56	Total NK cells [CD16+, CD56+]	7%	(5.6–30.9)

() normal ranges.

Table 4. Summary of Data Regarding Diabetes Mellitus

glucose tolerance test (GTT) performed at Feb.'98
75 g GTT

	before	30 min	60 min	120 min
PG (mg/dl)	118	218	304	418
IRI (μ U/ml)	10	14	20	48
U.S. (g/dl)	0	0	0.1	1.6

urinary C peptide

Aug.'96: 15–29 μ g/day (16–120)

Feb.'98: 22–32 μ g/day

glucagon test

serum C peptide (ng/ml) (before 0.6–2.8)

	before	3 min	6 min	10 min
Aug.'96:	1.9	3.9	4.3	3.8
Feb.'98:	2.4	4.8	5.5	5.5

insulin sensitivity by euglycemic clamp test

GIR (Glucose Infusion Test) (9.17–9.93)

Aug.'96: 3.02 mg/kg body weight/min

Feb.'98: 2.0 mg/kg body weight/min

on admission: Aug.'96

on readmission: Feb.'98

Insulin therapy was continued from admission to readmission because of secondary failure of sulfonylurea.

() normal range. PG: plasma glucose, U.S.: urine sugar.

gen level might play a role in the elevated PRL level in the current case. Chronic hypersecretion of LH, FSH, TSH, ACTH, GH and PRL might cause the slight swelling of anterior pituitary.

KS has also been reported to predispose to autoimmunity (1–6). Since autoimmune disease is preponderant in females, it has been suggested that the female-like hormonal condition is involved in the onset and/or progression of autoimmune disease. While a number of cases of KS associated with SLE (2, 3), PSS (4, 5) and PM (6) have been reported, MCTD has rarely been reported in association with KS. However, MCTD is defined as having characteristics of the three diseases, it is not surprising that KS is associated with MCTD. Ishihara et al (15) have reported a case of MCTD complicated with KS.

As with other collagen vascular disorders, the pathogenesis of MCTD seems to involve multiple factors. In the case of MCTD associated with KS, chronic estrogen stimulation, and decreased testosterone production could be possible factors. Ishihara et al (15) suggested that decreased DHEA-S in patients with KS may be involved in the association of autoimmune disease. In addition there is a report that patients with chromosomal aberrations have a higher incidence of autoim-

mune antibodies (16). According to a previous study (15), a decrease in the CD4/CD8 ratio was reported, suggesting that T cell abnormalities may be involved also in the development of autoimmune disease in KS. However, in the current case, the T cell population was normal. These discrepancies suggest that immunological abnormalities in patients with MCTD complicated with KS are not unique.

The current patient had the complication of DM. There are several reports indicating that the incidence of diabetes mellitus or diabetic glucose tolerance is high in patients with KS in Western countries. Nielsen et al (7) described the incidence as 39% (12 out of 31 cases) and Forbes and Engel (17) reported the incidence to be 15% (6 out of 41 cases). The incidence in Japan was reported as only 3.9% (17 cases out of 436), but still higher than in the normal population, 1.2% (18). It is worthwhile to note that cases where insulin therapy was required were more predominant in Japan than in Western countries (19). Careful surveys for diabetes may pick up mild cases of diabetes and an increased incidence in Japan. Differences in eating habits, frequency of obesity and genetic background must also be considered in explaining the difference in incidence between Japan and Western countries.

In the current case, insulin secretion was preserved and resistance to insulin was noted. He has had several backgrounds to having type 2 DM. His family history showed that he has a genetic factor to type 2 DM. He has also a twenty-year history of treatment with corticosteroids which are well known to induce diabetic status. Although patients with KS sometimes present as obese, which is one of aggravating factors for diabetes mellitus, the body mass index of the present patient was normal. Breyer et al (20) reported that insulin resistance in KS is attributed to decreased binding of insulin to its receptor. Therefore, in this patient, in addition to his genetic background and the long history of corticosteroid therapy, abnormal binding-activity of the insulin receptors may contribute to the insulin resistance.

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